

## CASE REPORT

# Rare occurrence of Whipple Disease in a young female patient with a fatal outcome

Emiliano Maresi <sup>a</sup>, Antonina Argo <sup>b,\*</sup>, Francesca Portelli <sup>a</sup>,  
Francesco Paolo Busardò <sup>b</sup>, Didier Raoult <sup>c</sup>, Hubert Lepidi <sup>c</sup>

<sup>a</sup> Department for Health Promotion, Section of Pathology, University of Palermo, Italy

<sup>b</sup> Department of Biopathology and Medical and Forensic Sciences, Section of Legal Medicine, University of Palermo, Italy

<sup>c</sup> Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UMR CNRS 6236/IRD 198, Université de la Méditerranée, Marseille, France

Received 10 January 2013; revised 3 April 2013; accepted 17 April 2013

Available online 24 May 2013

### KEYWORDS

Whipple Disease;  
*Tropheryma whippelii*;  
Epidemiology;  
Forensic pathology;  
Post-mortem diagnosis;  
Immunohistochemistry

**Abstract** Whipple Disease is a rare chronic multi-systemic disease caused by the ubiquitous environmental Gram-positive bacterium *Tropheryma whippelii*. It can be fatal if untreated. Here we describe the fatal outcome in a 27-year-old Caucasian female patient with a three-month history of persistent fever, anemia, weight loss and diarrhea. The final resolution of the diagnostic process was only reached after the patient's death thanks to autopsy. The case depicted is a classic Whipple Disease histologically characterized by digestive involvement based on positive periodic acid-Schiff (PAS) staining and immunohistochemical analysis for *T. whippelii* and systemic involvement (pericarditis, brain lipid storage, renal fat embolism). The case reported here is of interest because the patient was a woman and also young, characteristics which do not meet the classical epidemiological features of this elusive and troubling disease.

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## 1. Introduction

Whipple Disease (WD) was firstly described in 1907 by the American pathologist George Hoyt Whipple. He reported

\* Corresponding author. Address: Department of Biopathology and Medical and Forensic Sciences, Section of Legal Medicine, University of Palermo, via del Vespro 127, 90127 Palermo, Italy. Tel.: +39 0916553201.

E-mail address: [antonella.argo@unipa.it](mailto:antonella.argo@unipa.it) (A. Argo).

Peer review under responsibility of Forensic Medicine Authority.

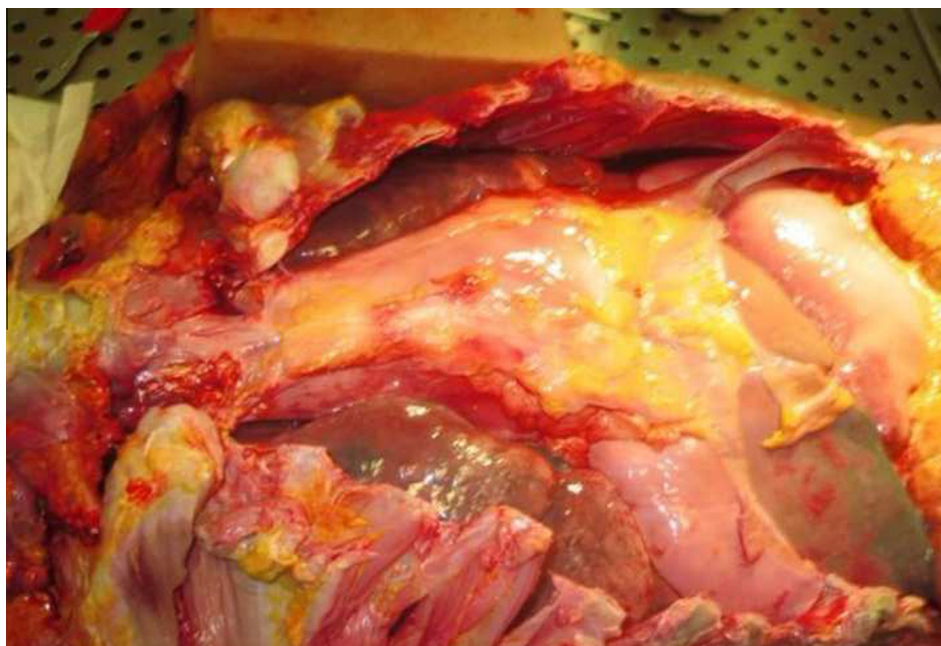


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the autopsy findings of a 36-year-old patient who had presented with weight loss, arthritis, cough, lymphadenopathy, fever, deposits of fat and fatty acids and foamy macrophages in the intestinal and mesenteric lymphatic tissue. It was suspected that he was suffering from a disorder of fat metabolism and his diagnosis was classified as a type of “intestinal lipodystrophy”.<sup>1</sup> In 1949, the content of the foamy macrophages was demonstrated to be periodic acid-Schiff (PAS) reagent positive<sup>2</sup> and in 1961 these PAS-positive inclusions in macrophages were demonstrated by electron-microscopy to represent bacteria, the so-called ‘bacillary’ or ‘bacilliform’ bodies<sup>3,4</sup>, thus establishing the bacterial etiology. The bacilli are rod-shaped and surrounded by a homogeneous cell wall within which is a typical trilaminar plasma membrane.<sup>5</sup> The targeting and



**Figure 1** Thickening of intestinal loops and mesentery and mesenteric lymph-nodes packed together.

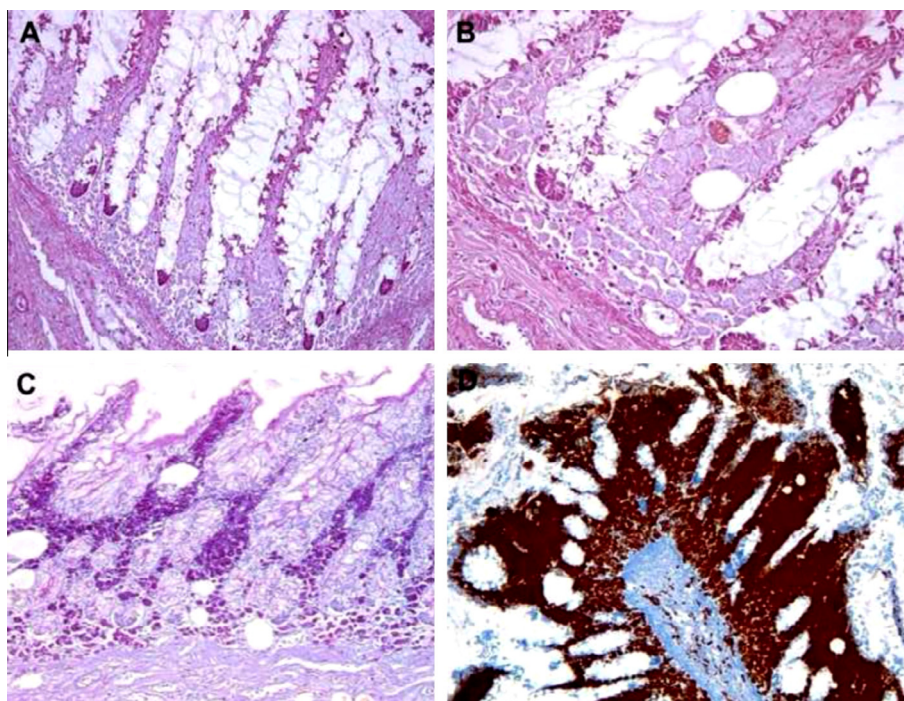


**Figure 2** Strong adhesions between the visceral pleura and the pericardial sac and between the pericardial sac and the diaphragm.

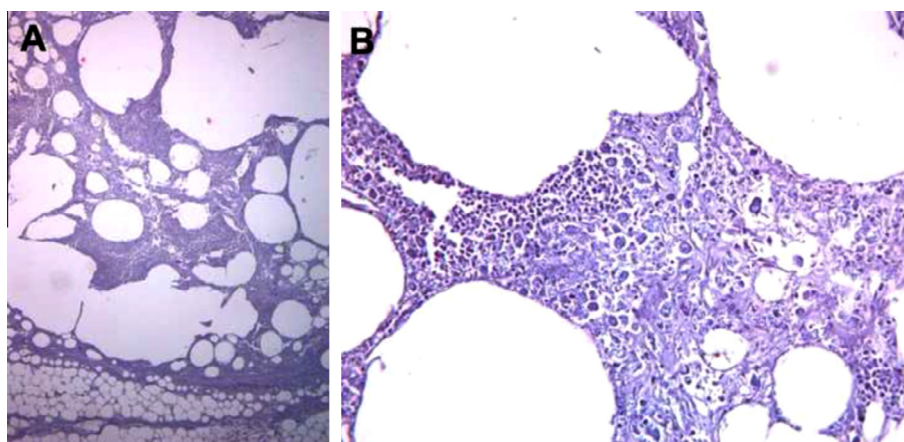
amplification of the bacterial 16S ribosomal RNA directly from tissues of patients with WD, by means of polymerase chain reaction (PCR)<sup>6,7</sup>, the successful isolation and establishment of a strain of the bacterium obtained from the mitral valve of a patient and the generation of specific antibodies against the bacterium in mice<sup>8</sup> helped in better understanding the pathogenesis of WD. At present PAS staining, PCR and specific immunohistochemical analysis performed directly on the patient's tissues represent the most accurate diagnostic tools. Despite its ubiquitous occurrence in the environment,

*Tropheryma whipplei*, the agent of WD, rarely causes disease, suggesting that more than just exposure is required for disease to occur. Moreover, it seems probable that there must be an immunogenetic susceptibility to the disease. Causative genes, predisposing immune factors, reservoir, transmission mechanism, and significance of possible asymptomatic carriers (in duodenal samples, stools, saliva, blood) have not yet been identified.<sup>9,10</sup> Even if WD can occur in people of all ages, it mostly affects men (86% of patients are male) of Caucasian origin (97% of the patients) and it seems to be more common





**Figure 3** Intestinal mucosa. A and B. Foamy macrophages crowding in the intestinal lamina propria (H&E, original magnifications  $\times 50$  and  $\times 100$ , respectively). C. Important infiltration of the lamina propria by numerous PAS-positive macrophages (PAS staining, original magnification  $\times 50$ ). D. Demonstration of *Tropheryma whipplei* by immunohistochemistry in macrophage cytoplasm (polyclonal rabbit anti-*Tropheryma whipplei* antibody used at a dilution of 1:2000, hematoxylin counterstain, original magnification  $\times 50$ ).



**Figure 4** Mesenteric lymph-nodes. A. Important secondary lymphangiectasia is seen in the pulp of the lymph node (H&E, original magnification  $\times 20$ ). B. Numerous PAS-positive macrophages are scattered in the lymph node (PAS staining, original magnification  $\times 40$ ).

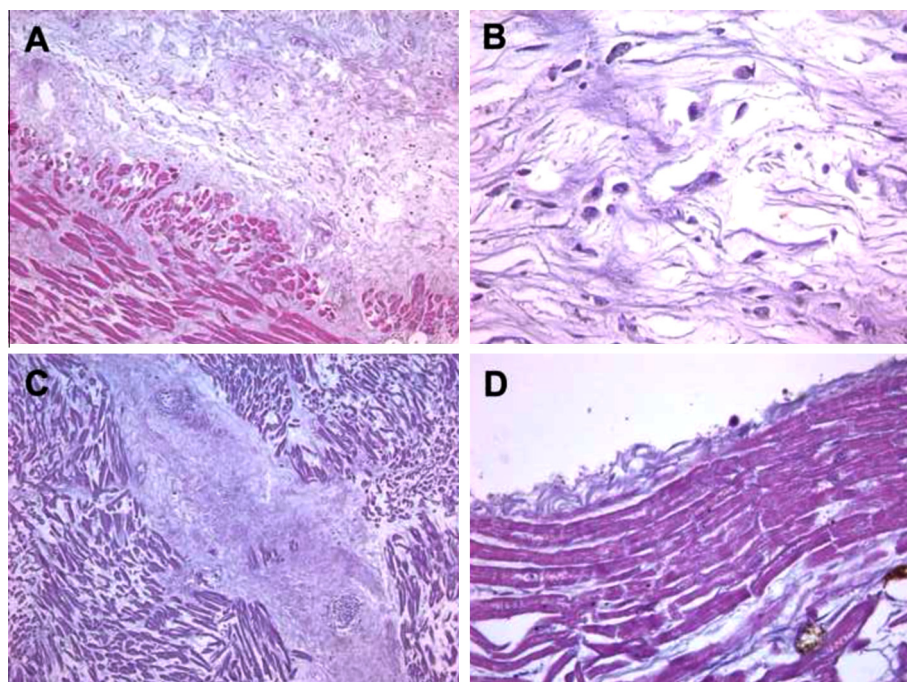
in farmers and people in farming-related trades.<sup>11,12</sup> The most common clinical presentation is a malabsorption syndrome, although patients may have also severe arthralgias for years before diarrhea develops. Cardiac and central nervous system involvement is also common. Because the illness is insidious in its onset, has a varied clinical presentation reflecting its systemic nature, and because it is rare, it is often diagnosed only late in its course, when antibiotic therapy may be less effective<sup>13</sup> or, as in this case, it may not be diagnosed until autopsy. Death in this case, which occurred only after six days of admission to hospital, is probably explained by the fact that

the patient was a woman and also young, making this case peculiar from an atypical epidemiological and clinical standpoint.

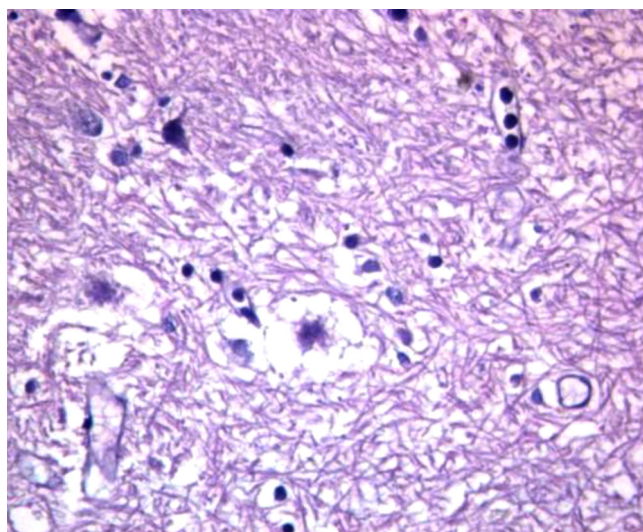
## 2. The case

This study reports the case of a 27-year-old Caucasian woman with a three-month history of persistent fever, anemia, weight loss (about 15 kg in three months) and diarrhea. She died 6 days after admission to hospital. She was affected by  $\beta$ -thal-

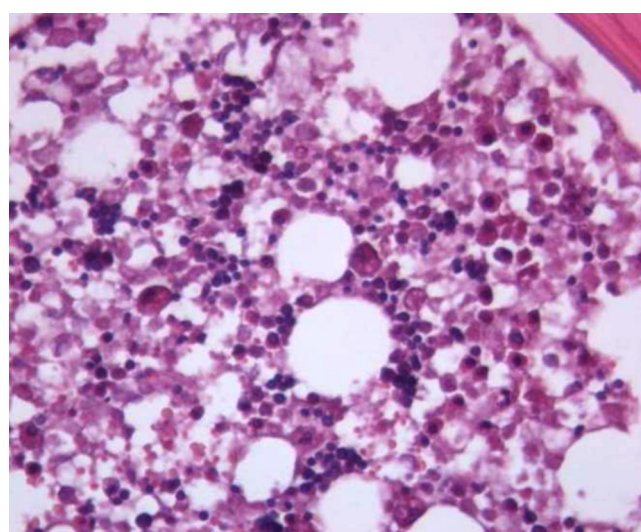




**Figure 5** Heart. A–D. Chronic fibro-adhesive pericarditis with many foamy histiocytes intermingled with fibroblasts and collagenous fibers. Parietal endocardium, slightly thickened, due to fibrosis (H&E, original magnifications  $\times 20$ ,  $\times 40$ ,  $\times 20$  and  $\times 20$ , respectively).



**Figure 6** Central nervous system. Lipid storage associated with cytotoxic and neuronal edema (H&E, original magnification  $\times 40$ ).

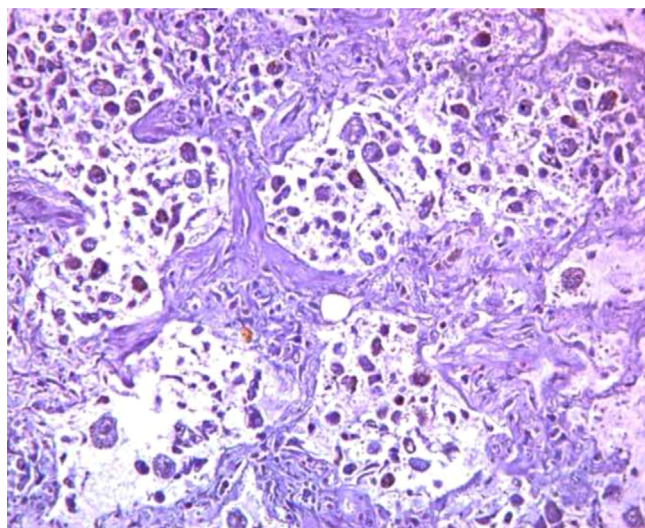


**Figure 7** Bone marrow. Hematopoietic tissue with a normal quantitative ratio of the erythropoietic and myelopoietic cell lines. Many erythrophagocytic and lipophagocytic macrophages (H&E, original magnification  $\times 40$ ).

asemia trait. Laboratory studies revealed hypochromic microcytic anemia with hemoglobin at 7.8 g/dl, hematocrit at 25.4%, white blood cell count at  $7.96 \times 10^3/\mu\text{l}$ , hyposideremia 8  $\mu\text{g/dl}$ , increased non-specific inflammatory markers (C-reactive protein 75.2 mg/l), erythrocyte sedimentation rate 48 mm, D-Dimer 324.9  $\mu\text{g/l}$ , fibrinogen (determined by the Clauss method) 550.5 mg/dl, hypoproteinemia 4.9 g/dl with reduced albumin/globulin ratio. Creatinine, transaminases, lactate dehydrogenase and coagulation profile were normal. Erythematous skin with painful subcutaneous nodules on the left leg was observed. Complement factor C3 was normal,

while C4 was slightly below the minimum of the range (11.9 mg/dl). The patient's clinical conditions worsened progressively with the decrease of hemoglobin to 6.4 g/dl, the onset of coagulation profile abnormalities (PT% 50.9%, INR 1.35), vomiting and respiratory insufficiency. Tumor markers, viral and parasitic serology, serology for celiac disease,  $\beta$ -hCG, p-ANCA, c-ANCA, ANA, ASMA and AMA were negative. Parasites in stools were absent. All screening exams for drugs of abuse were negative. An abdominal CT scan performed on





**Figure 8** Lungs. Severe plurifocal edema associated with desquamative macrophagic alveolitis. Modest plurifocal septal and peribronchovascular fibrosis with neutrophils, rare lymphocytes, histiocytes and proliferating fibroblasts. The capillary and arteriolar lumen is severely and extensively filled with lipid material. The interlobular septa appear enlarged due to lymphatic extravasation (H&E, original magnification  $\times 20$ ).

the 6th day showed an abundant peritoneal effusion. A further decrease of hemoglobin to 5.9 g/dl and a worsening of the coagulation profile (PT 31%, INR 1.99) were registered. Because of a suspected hemoperitoneum, an explorative minilaparotomy was performed without any evidence of ovarian bleeding areas or significant abdominal alterations. An abundant clear effusion was noted, with erythrocytes, lymphocytes, granulocytes, mesothelial cells and histiocytes without any neoplastic cells. Her clinical conditions got worse rapidly leading to shock. The patient was placed on assisted ventilation and died during the transfer to the Intensive Care Unit.

The woman's relatives lodged a complaint to the Court against the medical staff responsible for the woman's treatment because of the rapid worsening of her general conditions, in the absence of a diagnosis and a clear cause of death. The prosecutor ordered a forensic autopsy to clarify the cause of death and to evaluate the possible professional responsibility.

### 2.1. Macroscopic findings

At autopsy, the main macroscopic findings observed were intestinal loops dilated with thickened hard and rigid walls, mesentery also thickened, mesenteric lymph nodes enlarged and packed together (Fig. 1). Pleural and peritoneal effusions were noted. Strong adhesions were seen both between the visceral pleura and the pericardial sac and between the pericardial sac and the diaphragm (Fig. 2). The peritoneum covering the uterus was characterized by numerous hemorrhagic spots.

### 2.2. Microscopic findings

Sections of small intestine show numerous foamy macrophages infiltrated markedly and diffusely into the lamina propria, distorting the villi and numerous dilated lymphatic channels

(Fig. 3A and B). On PAS staining, the macrophages were filled with diastase-digested and non acid-fast stained PAS-positive granular material (Fig. 3C), due to the presence of bacilliform bodies. They were well-demonstrated by *T. whipplei*-specific immunohistochemistry (Fig. 3D). PCR assay for 16S ribosomal RNA genes of *T. whipplei* performed in the intestinal specimens was negative. The mesenteric lymph-node pulp was extensively infiltrated by PAS-positive macrophages (Fig. 4). The involvement of the pericardium and endocardium (Fig. 5), the central nervous system (Fig. 6), the bone marrow (Fig. 7) and the kidney mirrored the systemic nature of the infection. Microscopic findings of lungs are described in Fig. 8. These autopsical and histological findings are consistent with the diagnosis of WD.

## 3. Discussion and conclusions

Since 1907 autopsy findings have contributed to the illustration of WD, which can be fatal if untreated. WD is rare, though there is no valid estimate of its actual prevalence. Only about 1000 cases have been reported to date. In postmortem studies, the frequency of the disease is less than 0.1%.<sup>9</sup> It is often diagnosed at an advanced stage or in an extensive systemic form owing to its rarity, its broad spectrum of clinical presentations and the existence of forms with no clinical symptoms or histologically detectable involvement of the intestinal tract. In most cases, intermittent arthritis or arthralgia precedes the occurrence of other clinical signs by several years and such symptoms are reported in 80% of patients overall.<sup>12</sup> The case described here is a classic WD<sup>10</sup> marked by histological intestinal lesions in association with several clinical manifestations (pericarditis, brain lipid storage, renal fat embolism). The presence of subcutaneous nodules on the left leg is the only sign which can be clinically correlated with an eventual history of arthritis or arthralgia. The histological intestinal involvement is based on diastase-resistant, non-acid-fast, granular PAS-positive inclusions in foamy macrophages and specific immunohistochemical analysis. Furthermore the immunohistochemical analysis performed offers added specificity over PCR methods owing to the direct visualization of the bacillus in tissue sections. It also offers an increased sensitivity and specificity over the traditional non-specific PAS staining method.<sup>14–17</sup>

The degree and the extent of the endocardial and pericardial involvement do not appear related to either the duration or the clinical severity of the generalized disease process, confirming what is described in the series analyzed by McAllister and Fenoglio.<sup>18</sup> Anemia, hypoalbuminemia and an increase of non-specific inflammatory markers are very common clinical findings in classic WD. The pleural and peritoneal effusions were associated with an increase of CA-125 levels and ascribed to hypoalbuminemia and/or anemia secondary to malabsorption.

Even if the clinical presentation made the diagnosis of WD plausible, the epidemiological features, i.e. the female sex and especially the young age of the patient, were not characteristic of this pathology. In fact, although it occurs in people of all ages throughout the world, the typical patient is a middle-aged white man.<sup>9</sup> Regarding this, the literature review undertaken here (Table 1) confirms the rarity of this case related to the fact that the patient was a young woman. Furthermore, the extre-

**Table 1** Literature review.

Author	Cases	Age/Age range
Fisher and Whitman, 1954 <sup>19</sup>	One case, F	27 years
McAllister and Fenoglio, 1975 <sup>18</sup>	19 autopsical cases, all M	30–70 years
Clancy et al. 1975 <sup>20</sup>	One case, F	40 years
Crake et al. 1983 <sup>21</sup>	One case, M	37 years
Verhagen et al. 1996 <sup>22</sup>	One case, M	65 years
Puéchal, 2001 <sup>11</sup>	231 cases, 85% M	Age at diagnosis (mean, range): 50.4 years (20–82) Age at the onset of articular symptoms (mean, range): 40.3 years (15–75)
Baisden et al. 2002 <sup>14</sup>	18 cases (8 autopsical) M:F = 6:1	36–64 years
Lepidi et al. 2003 <sup>15</sup>	15 cases, M:F = 2:1	Mean age: 53.7 years Age range: 28–80 years
Yogi et al. 2004 <sup>23</sup>	One case, M	54 years
Iqbal et al. 2009 <sup>24</sup>	One case, M	58 years
Schaller and Carlson, 2009 <sup>25</sup>	One case, M	42 years
Vega-López et al. 2010 <sup>26</sup>	One case, F	47 years
Vangoitsenhoven et al. 2010 <sup>27</sup>	One case, M	43 years
Chhabria et al. 2010 <sup>28</sup>	One case, M	74 years
Pauletti et al. 2010 <sup>29</sup>	One case, M	53 years
Raheja et al. 2010 <sup>30</sup>	One case, F	56 years
Seneca et al. 2010 <sup>31</sup>	One case, M	39 years
Hoppé et al. 2010 <sup>32</sup>	5 cases, 4 M	Mean age: 50.4 yrs Age range: 38–67 years
Lagier et al. 2010 <sup>33</sup>	137 cases 113 with classic WD; 83 M; age range: 33–80 years 16 with endocarditis; all M; age range: 42–71 years 2 with uveitis, both F; 71 and 77 years 2 with adenopathy, both M; 33 and 39 years 2 with pulmonary involvement; F, 54 years; M, 57 years 2 with joint involvement; M, 70 years; M, 74 years	
Gaddy et al. 2011 <sup>34</sup>	One case, M	46 years
Blanc et al. 2011 <sup>35</sup>	One case, M	41 years
Longman et al. 2012 <sup>36</sup>	One case, M	53 years
Popović et al. 2012 <sup>37</sup>	One case, M	48 years
Renon et al. 2012 <sup>38</sup>	One case, M	61 years
Thinda et al. 2012 <sup>39</sup>	One case, M	50 years
Sparsa et al. 2012 <sup>40</sup>	2 cases, both M	42 and 53 years
Sung et al. 2012 <sup>41</sup>	One case, M	42 years
Neumann et al. 2012 <sup>42</sup>	One case, M	45 years

M: male; F: female; yrs: years.

mely rapid worsening of the clinical conditions in this case did not allow to complete the diagnostic process, thus leading to a rapid fatal outcome. The non-specific gastrointestinal symptoms and the variegated widespread clinical manifestations reflect the systemic nature of the infection and make it an insidious and elusive disorder.<sup>43</sup> Taking into account the difficulties related to the diagnostic process of such a rare disease, this case report describes the most relevant pathological features of the death of a young female patient and shows the significant aspects that every forensic pathologist should know about when giving medico-legal expertise in a suspected case of malpractice related to this rare disease.

### Funding

None.

### Conflict of interest

None declared.

### Ethical approval

Necessary ethical approval was obtained from the institute ethics committee.

### References

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull Johns Hopkins Hosp* 1907;**18**:382–91.
2. Black-Schaffer B. The tinctoral demonstration of a glycoprotein in Whipple's Disease. *Proc Soc Exp Biol Med* 1949;**72**:225–7.

3. Yardley JH, Hendrix TR. Combined electron and light microscopy in Whipple's Disease: demonstration of "bacillary bodies" in the intestine. *Bull Johns Hopkins Hosp* 1961;**109**:80–98.
4. Chears Jr WC, Ashworth CT. Electron microscopy study of the intestinal mucosa in Whipple's Disease. Demonstration of encapsulated bacilliform bodies in the lesion. *Gastroenterology* 1961;**41**:129–38.
5. Dobbins III WO, Kawanishi H. Bacillary characteristics in Whipple's Disease: an electron microscopy study. *Gastroenterology* 1981;**80**:1468–75.
6. Wilson KH, Frothingham R, Wilson JAP, Blitchington R. Phylogeny of the Whipple's-disease-associated bacterium. *Lancet* 1991;**338**:474–5.
7. Relman DA, Schmidt TM, MacDermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992;**327**:293–301.
8. Raoult D, Birg ML, La Scola B, Fournier PE, Enea M, Lepidi H, et al. Cultivation of the bacillus of Whipple's Disease. *N Engl J Med* 2000;**342**:620–5.
9. Fenollar F, Puéchal X, Raoult D. Whipple's Disease. *N Engl J Med* 2007;**356**:55–66.
10. Desnues B, Al Moussawi K, Fenollar F. New insights into Whipple's disease and *Tropheryma whipplei* infections. *Microbes Infect* 2010;**12**:1102–10.
11. Puéchal X. Whipple Disease and arthritis. *Curr Opin Rheumatol* 2001;**13**:74–9.
12. Puéchal X. Whipple's disease. *Ann Rheum Dis* Published Online First on January 3, 2013; doi: 10.1136/annrheumdis-2012-202684.
13. Dobbins III WO. The diagnosis of Whipple's Disease. *N Engl J Med* 1995;**332**:390–2.
14. Baisden BL, Lepidi H, Raoult D, Argani P, Yardley JH, Dumler JS. Diagnosis of Whipple Disease by immunohistochemical analysis: a sensitive and specific method for the detection of *Tropheryma whipplei* (the Whipple bacillus) in paraffin-embedded tissue. *Am J Clin Pathol* 2002;**118**:742–8.
15. Lepidi H, Fenollar F, Gerolami R, Mege JL, Bonzi MF, Chappuis M, et al. Whipple's Disease: immunospecific and quantitative immunohistochemical study of intestinal biopsy specimens. *Hum Pathol* 2003;**34**:589–96.
16. Dumler JS, Baisden BL, Yardley JH, Raoult D. Immunodetection of *Tropheryma whipplei* in intestinal tissues from Dr. Whipple's 1907 patient. *N Engl J Med* 2003;**348**:1411–2.
17. Misbah SA, Mapstone NP. Whipple's disease revisited. *J Clin Pathol* 2000;**53**:750–5.
18. McAllister Jr HA, Fenoglio Jr JJ. Cardiac involvement in Whipple's disease. *Circulation* 1975;**52**:152–6.
19. Fisher ER, Whitman J. Whipple's disease: report of case apparently cured and discussion of the histochemical features. *Cleve Clin Q* 1954;**21**:213–21.
20. Clancy RL, Tomkins WAF, Muckle TJ, Richardson H, Rawls WE. Isolation and characterization of an aetiological agent in Whipple's disease. *Br Med J* 1975;**3**:568–70.
21. Crake T, Sandle GI, Crisp AJ, Record CO. Constrictive pericarditis and intestinal haemorrhage due to Whipple's disease. *Postgrad Med J* 1983;**59**:194–5.
22. Verhagen WIM, Huygen PLM, Dalman JE, Schuurmans MMJ. Whipple's disease and the central nervous system. A case report and a review of the literature. *Clin Neurol Neurosurg* 1996;**98**:299–304.
23. Yogi T, Hokama A, Kinjo F, Tomiyama R, Koide M, Kishimoto K. Whipple's disease: the first Japanese case diagnosed by electron microscopy and polymerase chain reaction. *Intern Med* 2004;**43**:566–70.
24. Iqbal T, Karovitch A, Veinot J, Saginur R, Beauchesne L. Whipple's disease with constrictive pericarditis: a rare disease with a rare presentation. *Can J Cardiol* 2009;**25**:e89–91.
25. Schaller J, Carlson JA. Erythema nodosum-like lesions in treated Whipple's disease: signs of immune reconstitution syndrome. *J Am Acad Dermatol* 2009;**60**:277–88.
26. Vega-López CA, Carrillo-Ocampo JL, Castillo-Garcia J, González-de la Mora JJ, Alemán-Ortiz G, Romo-Aguirre C. Whipple's disease: a case report and review of the literature. *Rev Gastroenterol Mex* 2010;**75**:517–21.
27. Vangoitsenhoven R, Nijs J, Verbrugge H, Van Meerbeek J, Van den Bergh L. Whipple's disease. A classic case report and review of the literature. *Acta Gastroenterol Belg* 2010;**73**:392–6.
28. Chhabria MA, Dalal RJ, Desai DC, Deshpande RB. Whipple's disease. *J Assoc Physicians India* 2010;**58**:196–7.
29. Pauletti C, Pujia F, Accorinti M, Pauri F, Tinelli E, Bianco F, et al. An atypical case of neuro-Whipple: clinical presentation, magnetic resonance spectroscopy and follow-up. *J Neurol Sci* 2010;**297**:97–100.
30. Raheja AA, Lui YW, Pinzon-Ardila A, Lim RP, Sparr SA. Use of diffusion-weighted imaging in recurrent central nervous system Whipple's disease: a case report and review of the literature. *Clin Imaging* 2010;**34**:143–7.
31. Seneca V, Imperato A, Colella G, Cioffi V, Mariniello G, Gangemi M. Recurrent obstructive hydrocephalus as clinical onset of cerebral Whipple's disease. *Clin Neurol Neurosurg* 2010;**112**:717–21.
32. Hoppé E, Masson C, Audran M, Drillon M, Andreu M, Saraux A, et al. Whipple's disease diagnosed during biological treatment for joint disease. *Joint Bone Spine* 2010;**77**:335–9.
33. Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic *Tropheryma whipplei*. Clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. *Medicine* 2010;**89**:337–45.
34. Gaddy JR, Khan ZZ, Chaser B, Hal Scofield R. Whipple's disease diagnosis following the use of TNF- $\alpha$  blockade. *Rheumatology* 2012;**51**:946. <http://dx.doi.org/10.1093/rheumatology/ker387>.
35. Blanc F, Abdelghani KB, Schramm F, Jaulhac B, Chatelus E, Sordet C, et al. Whipple limbic encephalitis. *Arch Neurol* 2011;**68**:1471–3.
36. Longman RS, Moreira RK, Littman DR, Green PHR, Sethi A. *Gastroenterol Hepatol* 2012;**8**:60–3.
37. Popović DDJ, Spuran M, Jovanović I, Alempijević T, Djuranović N, Kovacevic N, et al. Whipple's disease: a case report. *Vojnosanit Pregl* 2012;**69**:522–5.
38. Renon VP, Appel-da-Silva MC, D'Incao RB, Lui Rm, Kirschnick B, Galperim B. Whipple's disease: rare disorder and late diagnosis. *Rev Inst Med Trop Sao Paulo* 2012;**54**:293–7.
39. Thinda S, Schoenberger SD, Kim SJ, Cohen DN, Tran U. *Arch Ophthalmol* 2012;**130**(9):1212. <http://dx.doi.org/10.1001/archophthalmol.2012.154>.
40. Sparsa L, Fenollar F, Gossec L, Leone J, Pennaforte JL, Dougados M, et al. Whipple Disease revealed by anti-TNF $\alpha$  therapy. *Rev Med Interne* 2012. <http://dx.doi.org/10.1016/j.rev-med.2012.10.371>, pii: S0248-8663(12)01111-3, Epub ahead of print.
41. Sung VW, Lyerly MJ, Fallon KB, Bashir K. Isolated CNS Whipple Disease with normal brain MRI and false-positive CSF 14-3-3 protein: a case report and review of the literature. *Brain Behav* 2012;**2**:838–43.
42. Neumann H, Neufert C, Vieth M, Siebler J, Mönkemüller K, Neurath MF. High-definition endoscopy with i-scan enables diagnosis of characteristic mucosal lesions in Whipple's disease. *Endoscopy* 2012;**44**:E217–8.
43. Patil S, Fantry GT. Clinical case review: connecting the dots: the many systemic manifestations of Whipple Disease. *Gastroenterol Hepatol* 2012;**8**:63–6.